REMARKS

The Official Action dated May 16, 2007 has been carefully considered. Additionally, the telephone interview of September 6, 2007 which Examiner Rooney and Examiner Haddad afforded the co-inventor Dr. Geza Bruckner, representative Carrie Benjamin and the undersigned representative is acknowledged and appreciated. Although a formal agreement was not reached during the interview, it is believed that the present Amendment, together with the Declaration Under C.F.R. 1.132 of the coinventor Dr. Dr. Sándor Sipka submitted herewith, overcomes the rejections, discussed in detail in the interview, and places this application in condition for allowance. Reconsideration is respectfully requested.

During the interview, the prior art of record, including Malling, Previte et al, Gereda et al and Oehling et al, were discussed in detail, with Examiner Rooney providing helpful comments on her interpretation of the references and Dr. Bruckner providing comments regarding the distinguishing features of the claimed processes over the teachings of the prior art. As a result of the discussions, it is believed that the arguments set forth herein respond fully to the prior art rejections and demonstrate the patentability of the claimed processes.

By the present Amendment, claims 1 and 22 are amended to recite a process for inhibiting development of allergic asthma, in accordance with the teachings in the specification, for example in the sentence bridging pages 2 and 3 and at page 4, lines 18-22. Claims 1 and 22 are also amended to recite that the irradiation-detoxified lipopolysaccharide is derived from extracted bacterial endotoxin and is operable to stimulate the Th 1 arm of the mammal's immune system, as, respectively, described at page 5, beginning at line 4 and previously set forth in claim 4. Finally, claim 25 is presented and includes limitations from previous claims 1, 4, 10 and 13 and the specification, for example in the sentence bridging pages 2 and 3, in the first full paragraph on page 4, and at page 5, beginning at line 4. It is believed that these changes do not

involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 1-5, 10, 13, 17-19 and 22-24 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserted that no in vivo studies were used and it is not clear that reliance on the in vitro data of IL-1 release reflects animal efficacy of the claimed therapeutic strategy as there is no correlation on the record between the in vitro studies and various methods of inhibiting allergic disease for humans, mammals or birds. The Examiner also asserted that the specification fails to provide guidance as how to totally (100%) inhibit all allergic disease in all mammals or birds.

This rejection is traversed and reconsideration is respectfully requested. Independent claims 1, 22 and 25 each recite a process for decreasing development of allergic asthma. Thus, the Examiner's comments relating to 100% inhibition and all allergic diseases are believed to be moot. Further, claims 1, 22 and 25 all recite a process step of exposing a neonatal or immature mammal to an irradiation-detoxified lipopolysaccharide (LPS) derived from extracted bacterial endotoxin, and reference to exposing a bird is omitted, whereby the Examiner's comments directed to birds are also believed to be moot.

Moreover, as a matter of Patent Office practice, a specification disclosure which contains a teaching of the manner and the process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis by Court). In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any

statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement, *supra.* at 370 (emphasis by Court).

Further, while the Examiner asserts that there is no evidence of record correlating IL-1 release in vitro data with the claimed methods, Applicants submit that it is well known that in vitro stimulation with LPS in human cells gives the same cytokine release pattern as in vivo stimulation of peripheral blood cells by LPS. In this regard, the Examiner's attention is directed to Lauw et al, *Infection and Immunity*, 68(3):1014-1018 (March 2000), a copy of which is provided herewith, which discloses that endotoxin LPS tolerance is characterized by a reduced capacity of monocytes to produce proinflammatory cytokines upon restimulaton in vitro. Attention is specifically directed to the Abstract and the Materials and Methods Section bridging pages 1014-1015. Attention is also directed to Salkowski, *Infection and Immunity*, 65 (8):3239-3247 (August 1997) and Henricson et al, *Infection and Immunity*, 58 (8):2429-2437 (August 1990), copies of which are provided herewith, both of which establish that LPS in vitro studies are recognized by those of ordinary skill in the art as screening procedures to determine mammal efficacy, including human efficacy. Accordingly, Applicants have provided evidence of record that one of ordinary skill in the art will recognize in vitro data as evidence of in vivo efficacy of the present methods.

As the present specification corresponds in scope to the terms used in the present claims for describing and defining the claimed processes, and Applicants have provided additional evidence correlating in vitro evidence to in vivo efficacy, the present specification must be taken as in compliance with the enabling requirement unless the Examiner provides acceptable evidence or reasoning which is inconsistent with the specification statements and the teachings of Lauw et al, Salkowski and Henricson et al submitted herewith. In the absence of such evidence

or reasoning, as here, the present specification must be taken as in compliance with the enabling requirement. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, is overcome. Reconsideration is respectfully requested.

Claims 1-5, 10, 13, 17-19 and 22-24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Malling et al in view of Previte et al, over Malling et al in view of Tarpley et al as evidenced by Schultz et al, over Malling et al in view of Previte et al and Matricardi et al, and over Malling et al in view of Matricardi et al and Tarpley et al as evidenced by Schultz et al. Claims 1-5, 10, 13, 17-19 and 22-24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gereda et al in view of Matricardi et al and Tarpley et al as evidenced by Schultz et al, and over Gereda al in view of Matricardi et al and Previte et al. Claims 1-5, 10, 13, 17-19 and 22-24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Oehling et al in view of Matricardi et al and Previte et al and over Oehling et al in view of Matricardi et al and Tarpley et al as evidenced by Schultz et al. Finally, claims 1-5, 10, 13, 17, 19 and 22-24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Tulic et al in view of Matricardi et al and Previte et al.

As will be set forth in detail below, these rejections are traversed and reconsideration is respectfully requested. Applicants submit that none of the cited combinations of references teach or suggest the combination of their teachings in a manner which would render obvious to one of ordinary skill in the art a process for decreasing development of allergic asthma as recited in any of independent claims 1, 22 or 25.

More particularly, independent claim 1 recites a process for decreasing development of allergic asthma. The process comprises exposing a neonatal or immature mammal to a irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system. Independent claim 22 recites a similar method

and specifies that the irradiation-detoxified LPS is derived from extracted *E. coli* bacteria endotoxin. Independent claim 25 also recites a process for decreasing development of allergic asthma. The process comprises exposing a neonatal or immature human of up to about two years of age to a irradiation-detoxified LPS derived from extracted bacterial endotoxin which is operable to stimulate the Th 1 arm of the human's immune system while reducing IL-1 stimulation caused by the native form of the LPS derived from extracted bacterial endotoxin. The exposing step comprises administering an aerosol spray composition of the irradiation-detoxified LPS derived from extracted bacterial endotoxin.

Importantly, as described beginning at page 4, line 1 of the present application, the present inventors have determined that irradiated LPS derived from extracted bacterial endotoxin has less stimulatory effect on interleukin 1(IL-1) production, thereby attenuating the effect, while maintaining the ability to stimulate the Th 1 arm of the immune system. As a result, the neonatal or immature mammal may be exposed to the irradiation-detoxified LPS to stimulate the Th 1 arm of the mammal's immune system, without causing significant stimulation of IL-1 production, either in the exposed mammal or of the immune system of mammals in the vicinity of exposure. Advantageously therefore, the exposure may be by administering an aerosol spray composition as recited in claims 10 and 25 without causing undesirable IL-1 immune system responses in the neonatal or immature mammal or other mammals in the immediate environment.

Attention is directed to the Declaration Under 37 C.F.R. 1.132 of the co-inventor Dr. Sándor Sipka submitted herewith. The Declaration describes in further detail the unique immune responses elicited by irradiation-detoxified (IR) lipopolysaccharide (LPS) which provide an unexpected and surprising improvement in the methods according to the present invention for decreasing development of allergic asthma in a neonatal or immature mammal. Particularly, the results set forth in the Declaration demonstrate that IR-LPS stimulates the production of IL-10

significantly better than native LPS. This is significant because IL-10 is the key cytokine for the suppression of allergic response and inflammation. Further, as noted in the specification, IR-LPS elicits lesser IL-1 beta production, and the Declaration further shows IR-LPS also elicits lesser TNF alpha production and IFN gamma production, indicating a positive but attenuated Th 1 response. IR-LPS elicits a lower percentage in CD-69 activation markers expressed by T lymphocytes. As CD-69 is elevated in asthmatic subjects, the lesser activation of this activation marker by IR-LPS indicates an attenuated asthmatic response. The IR-LPS also elicits a smaller increase in IL-4 production in atopic subjects but not in normal subjects, indicating a reduced Th 2 response. Accordingly, as the high concentration and long-lasting native endotoxin exposure can result in wheezing and rash in infancy, the use of IR-LPS diminishes these undesirable responses while still stimulating the production of the Th 1 related cytokines, IL-1 beta, TNF alpha and IFN gamma. This is a positive effect from the aspect of allergy prevention, with less side effects than would be produced with native LPS. Advantageously, for allergic neighbors living in the IR-LPS vicinity, their IL-4 (of the Th 2 arm) is not stimulated as intensively as it would be if native LPS were used.

The Declaration further states Dr. Sipak's opinion that these immune stimulating properties of IR-LPS are neither taught nor suggested by any of the prior art cited in the Official Action and therefore the prior art provides no suggestion of any benefit of using IR-LPS, particularly as compared with native LPS, in a method of decreasing development of allergic asthma, particularly by exposing a neonatal or immature mammal to IR-LPS.

The present methods are neither taught nor suggested by any of the primary references cited in the aforenoted rejections, or by modification of the teachings of any of the primary references in a manner suggested by the cited secondary references. Particularly, none of the cited prior art teaches or suggests that irradiated LPS derived from extracted bacterial endotoxin

has Th 1 stimulating properties, especially with attenuated IL-1 stimulating properties, and with reduced Th 2 stimulating properties as demonstrated in Dr. Sipka's Declaration, which would suggest its advantageous use in a method as presently claimed.

For example, Malling presents a review article focusing on the importance of bacterial infections in asthma and the clinical documentation of the efficacy of bacterial vaccines and discloses that, on the basis of current immunologic knowledge of the pathophysiological mechanisms of the allergic response, a possible roll for bacterial antigens in the treatment strategy is proposed (Background, page 214). The Examiner has referred to page 217, last paragraph, as teaching a process for inhibiting development of allergic diseases by exposing a neonatal or immature mammal to LPS derived from bacterial endotoxin wherein the LPS is adapted to stimulate the Th 1 arm of the immune system (see Official Action, page 8, lines 1-5). However, the last paragraph at page 217 of Malling discloses:

> "The prospects for future intervention strategy both to prevent the development of asthma and to interfere with the progression of mild asthma might take into account the possible adjuvantic role of bacterial infections in modifying the Th 2-skewed T-cell response in infants predisposed to atrophy. Bacterial products might be useful as adjuvants in optimizing the clinical efficacy of allergen-specific immunotherapy by a preferential induction of a Th-1 response."

Applicants find no teachings or suggestion in the referenced paragraph for exposing a neonatal or immature mammal to irradiation-detoxified LPS derived from extracted bacterial endotoxin as presently claimed or that such LPS is adapted to stimulate the Th 1 arm of the immune system. In fact, Applicants find no mention in the referenced paragraph to LPS or to LPS derived from extracted bacterial endotoxin as claimed. The broad reference to "bacterial products" does not teach or suggest LPS as presently claimed.

During the aforementioned interview, the Examiner asserted that "bacterial products" inherently encompasses LPS. Applicants do not disagree that LPS may be a component of a bacterial product. However, the generic reference to "bacterial products" does not teach or

suggest the claimed LPS, namely irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of a mammal's immune system, or even LPS derived from extracted bacterial endotoxin. Similarly, the generic "bacterial products" does not teach or suggest irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of a human's immune system while reducing IL-1 stimulation and Th 2 stimulation caused by native form of the LPS. In fact, Malling simply provides no teaching or suggestion of any LPS derived from extracted bacterial endotoxin. A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of various elements in a particular claim combination, *In re Newell*, 13 U.S.P.Q. 2d 1248 (Fed. Cir. 1989). Inherency and obviousness are entirely different concepts, *In re Rinehart*, 189 U.S.P.Q. 143, 148 (CCPA 1976). Thus, that LPS may be contained within Malling's generic "bacterial products" is irrelevant to the obviousness of the presently claimed processes, employing irradiated-detoxified LPS derived from extracted bacterial endotoxins.

The Examiner also pointed to Malling's reference to Holt et al at page 217 as having proposed the hypothesis of the importance of microbial stimulation via the respiratory and gastrointestinal mucosa during early childhood for the postnatal maturation of a Th-1 deviated immune response, and that the mechanism of Th-1 polarization could be initiated by microbial products such as bacterial lipopolysaccharides or specific immunostimulatory sequences (ISS) in bacterial DNA. Applicants have obtained a copy of the Holt et al publication referenced by Malling, namely Holt et al, Microbial Stimulation As An Aetiologic Factor in Atopic Disease, *Allergy*, 55:12-16 (1999), a copy of which is provided herewith. Holt et al specifically disclose:

> "Factors which influence quantitative and qualitative aspects of microbial stimulation via the respiratory and gastrointestinal mucosae during early childhood may have a major impact on the kinetics of postnatal maturation of Th-1 competence at a number of different levels. Theoretically, these include effects upon precursory populations within the mononuclear cell compartment in the bone marrow, thymus, etc. where signaling via microbial 'signature' molecules such as bacterial lipopolysaccharide, from commensal

> organisms, interacting with specific receptors such as CD 14 may influence various aspects of functional maturation" (page 15, left column).

Thus, Holt et al merely describe that bacterial LPS from microbial stimulation may influence postnatal maturation of Th-1 competence. In conclusion, Holt et al consider early vaccination with Th-1 stimulatory agents such as BCG as a potential preventive measure, but express "extreme caution" given the inherent complexities associated with the underlying cellular mechanisms (page 15, right column).

Thus, while Holt et al disclose that bacterial LPS from commensal organisms may influence various aspects of functional maturation of Th-1 competence, Applicants find no teaching or suggestion by Holt et al for administering LPS derived from extracted bacterial endotoxin, or specifically, irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, particularly while attenuating the IL-1 and Th 2 stimulation caused by the native form of the LPS. Accordingly, only in view of the present specification would one of ordinary skill in the art view Malling's reference to Holt et al, Holt et al's teachings or Malling's teachings as suggesting a process wherein a neonatal or immature mammal is exposed to LPS derived from extracted bacterial endotoxin. Absent the present specification, Malling is limited to bacterial vaccine products employing bacterial antigens (Background, page 214). One of ordinary skill in the art will appreciate that vaccines are artificial products containing suspensions of killed bacteria of effective antibody-producing allergens. Resulting antibodies, induced by the preventive vaccines, are able to attack pathogenic microbes. In contrast, LPS are present in the body and enter the blood where they act directly on CD14 receptors of blood monocytes, keeping the cells in a pre-activated state, ready to attack external bacteria. Additionally, cytokines, such as IL-1 beta, TNF alpha, etc., derived from blood monocytes have a broad immunostimulating effect on the Th 1 cell, thereby activating antibody production against invading bacteria. Malling's

teachings relating to bacterial vaccines, i.e., antigen products, do not teach or suggest administration of LPS, particularly irradiated LPS, derived from extracted bacterial endotoxin as recited in the present claims.

The Examiner asserted that Malling also discloses exposure to a neonatal or immature mammal by administering an aerosol spray composition comprising LPS, referring to page 216, right column, first paragraph (page 8 of the Official Action). The paragraph referenced by the Examiner discloses that children "received nonspecific immunotherapy and were treated with bacterial vaccine aerosols plus Fusafungin spray and Ketotifen, while other children were included in a specific immunotherapy program to receive *D. pteronyssinus*, and the two protocols were compared with a control group of children." However, Applicants find no teaching or suggestion in this description of LPS derived from extracted bacterial endotoxin, particularly irradiation-detoxified LPS derived from extracted bacterial endotoxin as required by the present claims. Further, this description does not teach or suggest a method for exposing a neonatal or immature human of up to about 2 years of age as required by claims 13 and 25.

The deficiencies of Malling are not resolved by the cited secondary references. Nor do the cited secondary references teach or suggest irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of a human's immune system, particularly while reducing IL-1 and Th 2 stimulation caused by native form of the LPS, or the use thereof in processes as presently claimed.

Specifically, Previte et al disclose detoxification of LPS of *Salmonella typhyimurium*, *S. enterifidis*, and *E. coli* by ionizing radiation. Previte et al are concerned with the lethality and pyrogenicity, and particularly the efficiency of the ionizing radiation in detoxifying the lethal determinants. Previte et al provide no teaching or suggestion relating to immune stimulatory properties of irradiated LPS. Previte et al disclose that an almost complete elimination of

lethality, referring to Figure 1, with only a slight decrease in antigenicity, referring to Fig. 3, and retention of pyrogenicity, referring to Fig. 2, indicates the existence of separate determinants responsible for these properties in the *S. typhyimurium* (page 1613, left column). However, Fig. 3 in fact discloses mean survival time of mice vaccinated with the LPS and challenged one day later, or six days later, with survivals/total shown. Thus, Previte et al do not demonstrate the immunosimultatory response of any irradiated LPS and particularly do not disclose that an irradiated LPS is operable to stimulate the Th 1 arm of the immune system, as recited in claims 1, 22 and 25, particularly while reducing IL-1 stimulation as recited in claim 25, or reducing Th 2 stimulation as shown in the Sipka Declaration. Thus, one of ordinary skill in the art would have had no motivation for employing the Previte et al materials in a method of decreasing development of allergic asthma, and therefore Previte et al provide no teaching or suggestion for resolving the deficiency of Malling in failing to teach or suggest exposing a neonatal or immature mammal to irradiated-detoxified LPS derived from extracted bacterial endotoxin.

Tarpley et al are directed to radiation sterilization of pharmaceutical products, particularly sterilization of heavily contaminated steroid suspensions, by gamma rays produced by kilocurie sources of radioactive cobalt and tantalum (page 309, left column). Tarpley et al are particularly concerned with techniques which may be substituted for more expensive aseptic procedures in providing such products (page 305, left column). The Examiner has asserted that one of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Tarpley et al in the bacterial immunotherapy method of inhibiting allergic disease of Malling because the bacterial immunotherapy method should be safe for use in infants and children and have no risk of infection. However, Tarpley et al have no concern regarding immune stimulatory effects of any bacteria included in their tested pharmaceutical products. To the contrary, Tarpley et al are simply concerned with sterilization of contaminated steroid suspensions and the radiation doses

of gamma rays produced by the kilocurie sources of radioactive cobalt and tantalum required for effective sterilization.

As Tarpley et al provide no teaching or suggestion of any bacterial product, and particularly irradiated LPS, for use in immunotherapy, or that the sterilization products described therein have any immunotherapy effect, Tarpley et al provide no motivation to one of ordinary skill in the art to have employed their sterilized steroid suspensions in a method of decreasing the development of allergic asthma. Further, one of skill in the art would have no motivation to employ steroid actives in place of the Malling bacterial products. Thus, Tarpley et al do not resolve the deficiencies of Malling and Previte et al.

Schultz et al similarly do not resolve these deficiencies. Schultz et al describe radiation degradation of polymethacrylates, and particularly the effect of radiation on molecular weight. The Examiner appears to use Schultz et al to interpret the radiation dose of Tarpley et al. It is therefore apparent that Schultz et al provide no teaching or suggestion for resolving the deficiencies of Malling and Tarpley et al in rendering the presently claimed processes obvious.

The Examiner relied on Matricardi et al as teaching at page 465 preventing allergy wherein an infant mammal is exposed to gram-negative microbial products. The Matricardi et al discussion to which the Examiner referred relates to administration of probiotics, i.e., living or inactivated organisms that are claimed to exert beneficial effects on health when ingested, the most common of which are lactobacilli and bifidobacteria, neither of which contain LPS since they are gram positive organisms. The Examiner again apparently asserted that LPS is inherent in such products. However, as noted, such gram positive organisms do not contain LPS, and the Matricardi et al probiotic products do not teach or suggestion LPS derived from extracted bacterial endotoxin as required by claims 1 and 25 or LPS derived from extracted E. coli bacteria

endotoxin as required by claim 22. Bacterial products containing LPS do not encompass LPS derived from the extracted materials recited in the present claims.

In fact, Matricardi et al themselves distinguish LPS from probiotics. See, for example, page 461, left column and page 467, right column, wherein LPS is acknowledged as isolated from outer membranes of gram negative bacteria. Importantly, Matricardi et al disclose that it was hypothesized that environmental LPS or endotoxin exposure would stimulate in humans Th 1 immune responses, but Matricardi et al acknowledge that LPS exerts severe endotoxin effects which limit its potential use as a therapeutic agent, whereby LPS derivatives which maintain immunostimulating properties but not its toxicity have been tested (page 468). Monophosphoryl lipid A (MPL) is one such molecule proposed as an adjuvant for vacccine antigens. Importantly, however, Matricardi et al provide no teaching or suggestion that an irradiated LPS derived from extracted bacterial endotoxin is operable to stimulate the Th 1 arm of a mammal's immune system, while avoiding the noted severe endotoxin effects, and particularly while reducing IL-1 stimulation caused by native LPS and attenuating the Th 2 arm response caused by the native form of the LPS. Thus, the present invention provides an important but unsuggested alternative to the MPL taught by Matricardi et al.

It should be noted that Matricardi et al's discussion of probiotics concludes that in view of a lack of compelling evidence that allergy is a disease caused by lack of bacterial stimulation and the mechanisms by which bacteria would prevent against allergy development, further studies are required before recommending microbial treatment to infants (page 465). Thus, Matricardi et al teach away from the Examiner's combination of references.

In view of the failure of Matricardi et al to teach, suggest or recognize that irradiated LPS as presently claimed exhibits a desirable combination of immune stimulatory effects, Matricardi et al do not teach or suggest that irradiated LPS derived from extracted bacterial endotoxin as

claimed is suitable for use in methods for decreasing development of allergic asthma according to the present invention. Previte et al's teaching of irradiated LPS does not resolve this deficiency in Matricardi et al as Previte et al fail to teach or suggest the immune stimulatory properties of irradiated LPS which render it advantageous for use in processes for decreasing development of allergic asthma. Similarly, Tarpley et al, even in view of Schultz et al, fail to provide this teaching, suggestion or recognition and therefore similarly fail to resolve the deficiencies of Matricardi et al.

Thus, Malling fails to teach or suggest a process for decreasing development of allergic asthma by exposing a neonatal or immature mammal to LPS derived from extracted bacterial endotoxin, and particularly irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system. While Previte et al teach irradiation of LPS, Previte et al provide no teaching or suggestion of the immunostimulatory properties of the irradiated LPS and particularly provide no teaching or suggestion that an irradiated LPS would be beneficial for use in decreasing development of allergic asthma disease. Tarpley et al, directed to sterilization of steroid products, similarly provide no teaching or suggestion regarding the immune stimulatory properties of irradiated LPS or decreasing development of allergic asthma. Finally, Matricardi et al hypothesized that environmental LPS or endotoxin exposure would stimulate in human Th 1 immune responses, Matricardi et al note that LPS exerts severe endotoxic effects which limits its potential use and Matricardi et al provide no teaching or suggestion of the immunostimulatory properties of irradiated LPS. Thus, none of the cited references teach or suggest that irradiation detoxified LPS derived from extracted bacterial endotoxin is operable to stimulate the Th 1 arm of a mammal's immune system, particularly while attenuating the Th 2 arm response, and is therefore advantageous for use in decreasing development of allergic asthma. In the absence of such a

teaching, one of ordinary skill in the art would have had no motivation for combining the selected teachings of the references to arrive at the claimed invention. The cited combinations of references based on Malling, in combination with any or all of Previte et al, Tarpley et al, Schultz et al and Matricardi et al, do not therefore render the presently claimed processes obvious, whereby the rejections under 35 U.S.C. §103 based on Malling have been overcome. Reconsideration is respectfully requested.

Gereda et al study the relation between house dust endotoxin exposure, type 1 T-cell development, and allergen sensitization in infants at high risk of asthma. Their study provides in vivo evidence that indoor endotoxin exposure early in life may protect against allergen sensitization by enhancing type 1 immunity. However, Applicants find no teaching or suggestion by Gereda et al relating to LPS derived from extracted bacterial endotoxin, irradiation-detoxified LPS derived from extracted bacterial endotoxin, or the immune stimulatory effects of irradiation-detoxified LPS derived from extracted bacterial endotoxin. Accordingly, Gereda et al provide no teaching or suggestion for a process as presently claimed and comprising the step of exposing a neonatal or immature mammal to irradiation-detoxified LPS derived from extracted bacterial endotoxin and operable to stimulate the Th 1 arm of the mammal's immune system, particularly while reducing IL-1 and Th 2 stimulation caused by native form of the LPS.

At page 16 of the Official Action, the Examiner asserted that Gereda et al teach exposing a neonatal or immature mammal to LPS derived from bacterial endotoxin. However, Gereda et al did not conduct any such process. To the contrary, Gereda et al merely assessed allergen sensitization in subjects while simultaneously collecting house dust samples from the subjects' households. No LPS derived from extracted bacterial endotoxin as claimed was employed nor was any neonatal or immature mammal exposed to LPS derived from extracted bacterial

endotoxin. The Examiner's interpretation of Gereda et al's methods to fit the process steps of the present claims is simply not supported by the Gereda et al disclosure.

Moreover, the deficiencies of Gereda et al are not resolved by Matricardi et al, alone or in combination with Tarpley et al or Previte et al. That is, as discussed in detail above, Matricardi et al hypothesized that environmental LPS or endotoxin exposure would stimulate in humans Th 1 immune responses that would protect against the development of atopy and asthma, but Matricardi et al also note that LPS exerts severe endotoxin effects which limit its potential use as a therapeutic agent. Thus, Matricardi et al do not provide any teaching or suggestion for using LPS derived from extracted bacterial endotoxin in a method for decreasing development of allergic asthma. Applicants again further note that Matricardi et al's discussion of exposure to gram negative bacteria or probiotics does not teach or suggest a process employing LPS derived from extracted bacterial endotoxin, notwithstanding the fact that gram negative bacteria contain LPS.

The deficiencies of Tarpley et al and Previte et al in failing to teach immunostimulatory properties of irradiated LPS as claimed are also discussed in detail above. Tarpley et al are particularly concerned with sterilized compositions of steroids and provide no teaching or suggestion regarding immunostimulatory properties of bacteria killed in such sterilization processes. Previte et al studied the efficiency of ionizing radiation in detoxifying the lethal determinants of LPS, but provide no teaching or suggestion regarding immunostimulatory properties of the irradiated LPS. Thus, one of ordinary skill in the art would have had no motivation or reason to employ irradiated LPS of Previte et al in a method for decreasing development of allergic asthma disease, particularly in view of the Matricardi et al teaching that LPS exerts severe endotoxin effects. Accordingly, Matricardi et al in combination with either Tarpley et al or Previte et al fails to resolve the deficiencies of Gereda et al and particularly fails

to teach or suggest to one of ordinary skill in the art a process for decreasing development of allergic asthma by exposing a neonatal or immature mammal to irradiation detoxified LPS derived from extracted bacterial endotoxin as recited in the present claims.

Thus, the various cited combinations of references based on Gereda et al fail to render obvious the processes for decreasing development of allergic asthma as presently claimed, whereby the rejections under 35 U.S.C. §103 based on Gereda et al in combination with Matricardi et al and Tarpley et al in view of Schultz et al, or Previte et al have been overcome. Reconsideration is respectfully requested.

Oehling et al describe a study of bacterial immunotherapy of childhood bronchial asthma. Eighty patients aged between 2 and 10 years at the time of immunotherapy took part in the study. The bacterial immunotherapy treatment employed a lyophilized bacterial vaccine containing 7 bacterial strains as described in Table 1 on page 178. The Examiner asserted that Oehling et al disclose exposing a neonatal or immature mammal to LPS derived from extracted bacterial endotoxin. However, while Oehling et al disclose administration of bacteria, Oehling et al provide no teaching or suggestion for administering LPS derived from extracted bacterial endotoxin as recited in claims 1, 22 and 25. In fact, Applicants find no teaching or suggestion by Oehling et al that LPS could be extracted from any of the bacteria employed in the bacterial vaccine taught by Oehling et al for effective use in a method of decreasing development of allergic asthma.

The deficiencies of Oehling et al are not resolved by any of Matricardi et al, Previte et al or Tarpley et al. The Examiner again relied on Matricardi et al as teaching the administration of living organisms as probiotics. However, Matricardi et al provide no teaching or suggestion for any method employing LPS derived from extracted bacterial endotoxin. To the contrary, Matricardi et al note that LPS exerts severe endotoxic effects which limit its potential effect as a

therapeutic agent, and Matricardi et al provide no teaching or suggestion that irradiated LPS avoids this toxicity while maintaining immunostimulating properties, and particularly maintaining Th 1 immunostimulating properties while attenuating IL-1 and Th 2 stimulating properties. Thus, Matricardi et al fail to resolve the deficiencies of Oehling et al.

Previte et al, as discussed above, studies the efficiency of ionizing radiation in detoxifying the lethal determinant of LPS of *Salmonella* strains and E. coli. However, Previte et al do not provide any teaching regarding immunostimulatory properties of irradiated LPS. Particularly, Previte et al do not teach that irradiated LPS is detoxified while maintaining Th 1 immunostimulating properties. Thus, Previte et al provide no motivation for using an irradiated LPS in place of the bacterial vaccines of Oehling et al. Consequently, Previte et al do not resolve the deficiencies of Oehling et al and Matricardi et al.

Finally, Tarpley et al teach that steroid preparations may be irradiation sterilized. However, Tarpley et al provide no teaching or suggestion that irradiated LPS is detoxified while maintaining Th 1 immunostimulatory properties, particularly while attenuating IL-1 and Th 2 immunostimulating properties. Thus, one of ordinary skill in the art would have had no motivation for employing the irradiation sterilized steroid preparations of Tarpley et al in place of the bacterial vaccines of Oehling et al. Tarpley et al therefore similarly fail to resolve the deficiencies of Oehling et al, Matricardi et al and Previte et al.

As none of the cited references employed in the rejections based on Oehling et al teach or suggest irradiated LPS derived from extracted bacterial endotoxin is detoxified while maintaining Th 1 immunostimulating properties, particularly while reducing IL-1 immunostimulating properties, one of ordinary skill in the art would have had no motivation to employ the claimed irradiation detoxified LPS in place of the bacterial vaccine of Oehling et al. Accordingly, Oehling et al in combination with any or all of Matricardi et al, Previte et al, or Tarpley et al in

view of Schultz et al, fail to render the presently claimed processes obvious. It is therefore submitted that the rejections under 35 U.S.C. §103 based on Oehling et al have been overcome. Reconsideration is respectfully requested.

Finally, Tulic et al disclose that exposure of young adult rats to native LPS can modify the development of allergic inflammation in vivo by two independent mechanisms. The Examiner asserted that Tulic et al teach that microbial infections early in infancy may protect from the later development if atopy and asthma such that the stimulus for normal postnatal maturation of the immunoinflammatory response may be provided by microbial stimulation. However, Tulic et al's hypothesis regarding microbial infections early in infancy provides no teaching or suggestion to one of ordinary skill in the art to expose a neonatal or immature mammal to LPS. Particularly, Tulic et al's study of mature rats provides no teaching or suggestion of a method of exposing a neonatal or immature mammal as presently claimed, absent the teachings of the present specification. While the Examiner asserted that Matricardi et al provide suggestion or motivation of such a method, Matricardi et al actually teach away from the use of LPS in view of its severe endotoxic effects. Matricardi et al's teaching of the severe endotoxic effects of LPS as employed by Tulic et al would have motivated one of ordinary skill in the art to proceed in a manner other than that taught by Tulic et al. While Matricardi et al note the LPS derivative MPL maintains immunostimulating properties of LPS but not its toxicity, Matricardi et al disclose the use of MPL in treating grass pollen sensitive subjects (page 468), not neonatal or immature mammals for decreasing development of allergy. Thus, Matricardi et al provide no teaching or suggestion for use of LPS in a method for decreasing development of allergy in neonatal or immature infants.

Finally, the deficiencies of Tulic et al and Matricardi et al are not resolved by Previte et al. As noted above, while Previte et al discuss the efficiency of ionizing radiation in detoxifying

the lethal determinants of LPS, Previte et al provide no teaching or suggestion regarding the immunostimulatory properties of irradiated LPS. Previte et al do not teach or suggest that irradiated LPS may be detoxified while maintaining the Th 1 immunostimulating property advantageous for use in the present processes, particularly while attenuating IL-1 and Th 2 immunostimulating properties. In view of the failure of Previte et al to teach these properties, one of ordinary skill in the art would have had no motivation, absent the present specification, for employing irradiated LPS in a method for decreasing development of asthma, particularly by exposing a neonatal or immature mammal to such irradiation detoxified LPS. Thus, Previte et al fail to resolve the deficiencies of Tulic et al and Matricardi et al, whereby this combination does not render obvious to one of ordinary skill in the art the presently claimed processes for decreasing development of allergic asthma. Accordingly, the rejection under 35 U.S.C. §103 based on Tulic et al has been overcome. Reconsideration is respectfully requested.

In each of the rejections under 35 U.S.C. §103 set forth in the Official Action, the Examiner has failed to establish that one of ordinary skill in the art would have recognized that an irradiation detoxified LPS derived from extracted bacterial endotoxin is operable to stimulate the Th 1 arm of the immune system, particularly while reducing the IL-1 immune response. In view of this deficiency in the teachings of the cited prior art, one of ordinary skill in the art would have had no motivation for employing irradiation detoxified LPS derived from extracted bacterial endotoxin in any of the methods taught or suggested by the primary references. In fact, Matricardi et al teach away from the use of LPS owing to its severe endotoxic effects. While Previte et al disclose that lethal determinants of LPS may be detoxified by irradiation, Previte et al provide no teaching or suggestion regarding immunostimulatory properties of irradiated LPS. While the Examiner may assert that the immunostimulatory properties of irradiated LPS are inherent in the irradiated LPS of Previte et al, inherency and obviousness, as noted above, are

entirely different concepts. None of the cited references recognize or distinguish between the positive Th 1 stimulatory effects and Th 2 attenuating effects of irradiation detoxified LPS. A view that success would have been inherent cannot substitute for a showing of a reasonable expectation of success, *In re Reinhardt, supra.* While the Examiner may have asserted that the detoxification of the irradiated LPS would have motivated one of ordinary skill in the art to employ the LPS in methods taught or suggested by the primary references, the Examiner's reasoning is misplaced as there is no teaching or suggestion that the irradiated LPS has desirable immunostimulating properties suitable for use in such methods. Accordingly, the presently claimed processes are nonobvious over the cited prior art combinations of references, wherein the rejections under 35 U.S.C. §103 have been overcome.

It is therefore believed that the above represents a complete response to the rejections under 35 U.S.C. §§103 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 04-1133.

Respectfully submitted,

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